Association Between Pulmonary Fibrosis and Coronary Artery Disease

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Background: Pulmonary fibrosis and atherosclerosis have many similarities at the histopathologic level. Moreover, fibrotic lung diseases exhibit systemic effects and have the potential to affect the vasculature beyond the lung. The existence of a relationship between the two, however, has not been studied.

Methods: To investigate whether fibrotic lung disorders may predispose to atherosclerosis, we conducted a cross-sectional study of 630 patients referred for lung transplantation evaluation at a university hospital. We compared the prevalence of angiographic coronary artery disease (CAD) in patients with fibrotic vs nonfibrotic lung diseases.

Results: Fibrotic lung diseases were associated with an increased prevalence of CAD compared with nonfibrotic diseases after adjustment for traditional risk factors (odds ratio, 2.18; 95% confidence interval, 1.17-4.06). The magnitude and significance of this association were maintained when only nongranulomatous fibrotic disease or its subset, idiopathic pulmonary fibrosis, was examined. The strength of the relationship between fibrotic disorders and CAD increased when multivessel disease was analyzed (odds ratio, 4.16; 95% confidence interval, 1.46-11.9). No significant association was detected for granulomatous fibrotic disorders (odds ratio, 1.56; 95% confidence interval, 0.47-5.16; P = .47), although this subgroup had fewer cases of CAD for analysis.

Conclusions: These findings support an association between fibrotic lung disorders and CAD. Further research is necessary to confirm this relationship and to explore the pathologic processes underlying, and potentially linking, these 2 conditions.

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Atherosclerosis results from an excessive inflammatory and/or fibroproliferative response to various insults to the endothelium and smooth muscle of the arterial wall.1 The pathogenesis of the atherosclerotic lesion involves recruitment of leukocytes into the vascular intima, accumulation of cholesterol-laden mononuclear cells, vascular smooth muscle cell proliferation and migration, deposition of collagen-rich extracellular matrix, and neovascularization to support the evolving fibroproliferative process.1-Fibrotic lung diseases have many pathologic parallels to atherosclerosis.1 In these heterogeneous disorders, there is also recruitment of leukocytes into the pulmonary compartment, destruction of alveolar-capillary units by the inflammatory process, and subsequent stimulation of pulmonary myofibroblasts to produce extracellular matrix.2,3 New blood vessel formation similarly supports myofibroblast activity, leading to the replacement of functional lung parenchyma by fibrous tissue.2,3

The pathologic similarities between these 2 conditions suggest that they could be linked. Furthermore, the finding of elevated proinflammatory factors4-6 and acute phase reactants4,7 in the sera of patients with fibrotic lung diseases provides potential mechanisms through which these disorders could promote atherogenesis. To our knowledge, the relationship between pulmonary fibrosis and atherosclerosis has not been explored. We examined a cohort of patients with end-stage lung disease to investigate whether fibrotic lung disorders may predispose to coronary artery disease (CAD).

Methods

Study Population

The study population included all consecutive patients evaluated for lung transplantation at the Hospital of the University of Pennsylvania in whom coronary angiography was performed between July 1, 1992, and December 31, 2000. Two investigators (J.R.K., D.A.Z.) abstracted relevant data from detailed clinical forms completed for each patient at the time of transplantation evaluation. Patients referred to the clinic...
because of chronic rejection of a previous lung transplant or radiation-induced pulmonary fibrosis were excluded. Coronary angiography was performed routinely in patients older than 40 years. In younger patients with coronary risk factors, angiography was ordered at the discretion of the transplantation pulmonologist. Patients with cystic fibrosis, who were generally too young to undergo angiography, were also excluded from analysis.

### CLASSIFICATION OF LUNG DISORDERS

The fibrotic lung disorders category comprised all patients diagnosed as having fibrosing interstitial lung disease at the time of evaluation. Interstitial lung disease is a diverse group of disorders characterized by varying degrees of interstitial inflammation and fibroproliferation. The extent to which the pathologic process leads to fibrotic replacement of the lung parenchyma is highly variable. In our population, however, equation of interstitial lung disease with pulmonary fibrosis was justified because these diseases had progressed to diffuse, end-stage fibrosis. The reference category, nonfibrotic disorders, consisted of patients with diseases in which fibroproliferation is not a dominant pathogenic feature, mainly disorders of the airways and pulmonary vasculature. Patients with pulmonary fibrosis were subdivided into nongranulomatous and granulomatous categories on the basis of their evaluation diagnosis, and the former group was further categorized into an idiopathic pulmonary fibrosis (IPF) subset. To ensure a classification of IPF consistent with the currently accepted clinicopathologic system, 3 pulmonologists (D.A.Z., R.M.K., and S.M.A.) reviewed the primary medical records of all patients with nongranulomatous interstitial lung disease and revised the evaluation form diagnoses by consensus.

### DEFINITION OF POTENTIAL CONFOUNDING FACTORS

The following definitions were used for various potential confounding factors: hypertension is a history of documented high blood pressure (≥140/90 mm Hg) or treatment with antihypertensive medication; hypercholesterolemia is a serum total cholesterol level of 240 mg/dL or higher (≥6.21 mmol/L) or use of lipid-lowering therapy; glucose intolerance is a fasting serum glucose level of 140 mg/dL or greater (≥7.8 mmol/L) or a random serum glucose level of 200 mg/dL or greater (≥11.1 mmol/L) or use of oral hypoglycemic or insulin therapy (if receiving systemic glucocorticoid therapy, during maintenance dosing only); family history is a history of CAD in a first-degree relative younger than 60 years; and coexisting systemic inflammatory disease is a diagnosis of collagen vascular disease, inflammatory bowel disease, or hepatic cirrhosis.

### DEFINITION OF END POINTS

Coronary artery disease was defined as the presence of 1 or more 50% or greater stenoses in an epicardial coronary artery, as reported in the cardiac catheterization summary reviewed for each patient. The secondary end point of multivessel CAD was used to classify patients with 50% or greater lesions in 2 or more major epicardial vessel distributions. Patients with a documented history of CAD occurring before the radiographic detection or formal diagnosis of the pulmonary disorder prompting transplantation evaluation were excluded from analysis.

### COMPARISONS

In the primary analysis, we compared the prevalence of CAD in fibrotic vs nonfibrotic lung disorders. Secondary analyses focused on subgroups of fibrotic disease. Granulomatous and nongranulomatous fibrosis—and the nongranulomatous subset, IPF—were each compared with nonfibrotic disorders. Where numbers were sufficient for analysis, similar comparisons were performed for multivessel CAD.

### STATISTICAL ANALYSIS

Categorical variables are reported as percentages, and continuous variables are presented as medians and ranges. The χ² test or Fisher exact test and the Wilcoxon rank sum test were used in comparisons of categorical variables and nonnormally distributed continuous variables, respectively.

To control for confounding, we identified 11 covariates routinely documented in the transplantation evaluation forms that are established or potential risk factors for CAD, including the binary variables sex, race, hypercholesterolemia, hypertension, glucose intolerance, family history of premature CAD, coexisting systemic inflammatory disease, cytomegalovirus seropositivity, and oral glucocorticoid therapy; cigarette smoking as an interval variable by tertile of cumulative pack-years (≤20, 21–60, >60 pack-years); and age as a continuous variable. In the primary comparison, the number of outcomes permitted fitting a full logistic regression model containing the exposure plus all prespecified covariates. We then serially eliminated covariates whose removal resulted in the smallest changes in the magnitude of the odds ratio (OR) until no additional covariate could be dropped without altering this effect estimate by 10% or more. In the remaining analyses, fewer outcomes were assessed. The 10% change-in-estimate cutoff value was again used, this time to identify univariable, and retain important multivariable, confounders for the final model. Covariate inclusion in the multivariable model continued until no single covariate capable of substantively affecting the OR could be added. Analyses were performed using SAS statistical software (SAS version 6.2; SAS Institute Inc, Cary, NC).

Of 694 study-eligible patients, 7 (4 with pulmonary fibrosis and 3 without) were excluded because clinical cardiac disease had predated the detection of lung disease. An additional 37 patients did not undergo coronary angiography, leaving 630 patients for analysis. Compared with this cohort, the non-angiography group was younger (median, 37 years; P < .001), more often female (68%; P < .001), smoked less (median, 0 pack-years; P = .04), and had fewer remaining coronary risk factors (67% without hypertension, glucose intolerance, hypercholesterolemia, or a positive family history; P = .002). Eighty-four percent of patients not receiving angiography had nonfibrotic disorders vs 70% of those receiving angiography (P = .03).

Table 1 gives the distribution of pulmonary disorders in the study cohort. The clinical and demographic characteristics of patients with fibrotic vs nonfibrotic disorders are given in Table 2. In patients with fibrotic lung disorders, male sex, glucose intolerance, cytomegalovirus seropositivity, and use of oral glucocorticoids were significantly higher and white race, family history, and pack-years smoked were significantly lower. This was also the case for nongranulomatous fibrosis vs the reference group, except that coexisting inflammatory disease, but not family history, was significantly more prevalent in the nongranulomatous subset. In turn, the granulomatous subgroup was younger and had fewer whites, pack-years smoked, and positive family histories but more glucocorticoid therapy and glucose intolerance than the nonfibrotic group.

Figure 1 shows the prevalence of CAD in the various lung disease groups. Coronary artery disease was most prevalent in the nongranulomatous subgroup and least
In this study, we found a strong association between fibrotic lung disorders and CAD after adjusting for multiple coronary risk factors. This association remained significant and consistent in magnitude in the subgroup with nongranulomatous fibrosis. It was also maintained in the subgroup with IPF, which constituted a large proportion of the patients in the nongranulomatous category. For fibrotic lung disorders and the nongranulomatous subgroup, the association became more pronounced when multivariable adjustment was used as the outcome measure. By contrast, we could not demonstrate a significant association for the subgroup with granulomatous fibrosis. The observed effect in the latter was also positive, but it was surrounded by broad confidence bounds. In the granulomatous subgroup, younger age, lower cigarette consumption, and less frequent family history may have contributed to the smaller end point prevalence. Removal of this subgroup, in fact, led to small increases in the associations found for the nongranulomatous and IPF subsets. Our data, however, cannot establish whether the lack of a significant association for granulomatous fibrotic processes stems exclusively from these factors, reflects the weaker association between these diseases themselves and CAD, or is a mixture of these and other factors.

The observed association between fibrotic lung disorders and CAD emerged only after correction for differences in the distribution of coronary risk factors. Cumulative exposure to tobacco was markedly higher in the granulomatous subgroup. In the case of coronary revascularization for critical CAD, the higher rate observed for nongranulomatous fibrosis relative to the reference group proved to be statistically significant (3.6% vs 0.7%; \( P = .03 \)).

The crude and adjusted ORs of CAD for fibrotic vs nonfibrotic disorders are given in Table 3. No significant relationship was observed in the smoking-adjusted comparison of any CAD. Adjustment for smoking, however, yielded a statistically significant association between fibrotic disorders and CAD. This relationship remained significant after multivariable adjustment for the aggregate of measured confounding (OR, 2.18; 95% confidence interval [CI], 1.17-4.06). A stronger relationship was observed in the analysis of multivessel CAD, which also proved significant in the smoking-adjusted comparison and the multivariable-adjusted comparison (OR, 4.16; 95% CI, 1.46-11.9).

In Table 4, the nongranulomatous fibrosis subgroup is compared with the nonfibrotic group. There was a significant association for any CAD and multivessel disease after multivariable adjustment. The magnitude of the association with CAD was slightly greater than that observed in the primary comparison (OR, 2.37; 95% CI, 1.22-4.60), and that for multivessel disease was again close to twice as large for any CAD. Further analyses also showed a significant association between IPF and CAD after multivariable adjustment (OR, 2.31; 95% CI, 1.11-4.82). In contrast, there was no significant association between granulomatous fibrosis and CAD (OR, 1.56; 95% CI, 0.47-5.16). Multivariable-adjusted ORs of CAD for fibrotic lung disorders and its subsets are summarized in Figure 2.

**Table 1. Pulmonary Diagnoses in the Study Cohort**

<table>
<thead>
<tr>
<th>Pulmonary Diagnosis</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nongranulomatous ILD</td>
<td>285 (45.7)</td>
</tr>
<tr>
<td>IPF/primary UIP</td>
<td>76 (12.1)</td>
</tr>
<tr>
<td>Other idiopathic interstitial pneumonia*</td>
<td>12 (1.9)</td>
</tr>
<tr>
<td>CVD associated†</td>
<td>14 (2.2)</td>
</tr>
<tr>
<td>Pneumoniosis (asbestos/silica)</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Drug induced</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Other secondary interstitial pneumonia‡</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>Nongranulomatous ILD</td>
<td>1113 (17.9)</td>
</tr>
<tr>
<td>Granulomatous ILD</td>
<td>379 (60.2)</td>
</tr>
<tr>
<td>Sarcoidealitis</td>
<td>58 (9.2)</td>
</tr>
<tr>
<td>Pulmonary hypertension§</td>
<td>56 (8.9)</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
<td>8 (1.3)</td>
</tr>
<tr>
<td>Obiliterative bronchiolitis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Nongranulomatous ILD</td>
<td>444 (70.5)</td>
</tr>
</tbody>
</table>

Abbreviations: AIAD, \( \alpha \)-1-antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; CVD, collagen vascular disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

*Includes desquamative interstitial pneumonia, nonspecific interstitial pneumonia, respiratory bronchiolitis interstitial pneumonia, and unclassified.
†Includes secondary UIP, nonspecific interstitial pneumonia, and bronchiolitis obiliterans organizing pneumonia.
‡Includes post–acute respiratory distress syndrome and alveolar microthiasis.
§Primary or secondary.
CAD, various epidemiologic risk factors can produce inflammatory response and eventuates in fibroproliferation.1-3 In initiated by local injury, which results in a sustained inflammatory response to the same or different stimuli in affected individuals. The third is that the 2 processes could be linked by a causal relationship.

Three explanations may be advanced to account for the association reported herein. One possibility is that a common offending agent gives rise to both processes. A second is the presence of a general proclivity to fibrosis in individuals. The third is that the 2 processes could be linked by a causal relationship.

The first 2 explanations are suggested by similarities in the cellular pathologic features of atherosclerosis and chronic fibrosing lung diseases.1 Both are thought to be initiated by local injury, which results in a sustained inflammatory response and eventuates in fibroproliferation.1-3 In CAD, various epidemiologic risk factors can produce endothelial injury and atherosclerosis in animal models.1 But as many as one half of patients with CAD may have no detectable clinical predisposition.1,13 Similarly, whereas in some forms of fibrotic lung disease the injurious factor is well established,6 for IPF and sarcoidosis the nature of the injurious stimulus remains undefined.3,14 These unresolved questions have led to consideration of infectious etiologies, a notion bolstered in atherosclerosis by recent reports of significant associations with a variety of organisms.15 However, the results of histopathologic studies13 and analyses13-17 of helper T-cell cytokine profiles show that the patterns of leukocyte involvement in pulmonary fibrosis and atherosclerosis are distinct. These important differences in immunologic response make it improbable that

### Table 2. Clinical and Demographic Characteristics of 630 Patients With Fibrotic vs Nonfibrotic Disorders

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fibrotic Disorders (n = 186)</th>
<th>Nonfibrotic Disorders (n = 444)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 113)</td>
<td>NG (n = 55)</td>
<td>G (n = 58)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>51 (27-65) 55 (28-65) 49 (27-63)*</td>
<td>54 (19-66)</td>
<td>.06</td>
</tr>
<tr>
<td>Male, %</td>
<td>52.2*</td>
<td>60.2*</td>
<td>39.7</td>
</tr>
<tr>
<td>White, %</td>
<td>65.1*</td>
<td>81.4*</td>
<td>39.7*</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>23.7</td>
<td>16.8</td>
<td>34.2</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>33.1</td>
<td>32.7</td>
<td>33.8</td>
</tr>
<tr>
<td>Total cholesterol level, median (range)</td>
<td>207 (108-317)</td>
<td>208 (127-317)</td>
<td>206 (108-312)</td>
</tr>
<tr>
<td>Glucose intolerance, %</td>
<td>17.2*</td>
<td>14.2*</td>
<td>21.9*</td>
</tr>
<tr>
<td>Smoking, median (range), pack-years</td>
<td>10 (0-111)*</td>
<td>18 (0-111)*</td>
<td>1 (0-105)*</td>
</tr>
<tr>
<td>Family history, %</td>
<td>7.1†</td>
<td>8.9</td>
<td>4.2†</td>
</tr>
<tr>
<td>Coexisting inflammatory disease, %‡</td>
<td>5.9</td>
<td>8.8§</td>
<td>1.4</td>
</tr>
<tr>
<td>CMV seropositive, %</td>
<td>65.2§</td>
<td>65.8†</td>
<td>64.3</td>
</tr>
<tr>
<td>Oral glucocorticoid use, %</td>
<td>73.7*</td>
<td>70.8*</td>
<td>78.1*</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; CI, confidence interval. *P < .001 vs nonfibrotic group. †P < .05 vs nonfibrotic group.
‡Includes collagen vascular disease, inflammatory bowel disease, and hepatic cirrhosis. §P < .01 vs nonfibrotic group.

### Table 3. Coronary Artery Disease in Fibrotic vs Nonfibrotic Disorders

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fibrotic vs Nonfibrotic</th>
<th>Nonfibrotic vs G</th>
<th>Fibrotic vs G</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CAD</td>
<td>1.19 (0.70-2.02)</td>
<td>.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>1.29 (0.75-2.22)</td>
<td>.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking adjusted</td>
<td>1.83 (1.02-3.28)</td>
<td>.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariable adjusted*</td>
<td>2.18 (1.17-4.06)</td>
<td>.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>2.04 (0.86-4.80)</td>
<td>.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>2.21 (0.93-5.23)</td>
<td>.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking adjusted</td>
<td>3.35 (1.31-8.61)</td>
<td>.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariable adjusted†</td>
<td>4.16 (1.46-11.9)</td>
<td>.008</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; CI, confidence interval. *Adjusted for age, race, smoking, and family history. Model inclusion of sex, hypertension, hypercholesterolemia, glucose intolerance, oral glucocorticoid use, coexisting inflammatory disease, and cytomegalovirus seropositivity, either individually or in combination, did not substantially modify the odds ratio.
†Adjusted for glucose intolerance, smoking, family history, and cytomegalovirus positivity. Model inclusion of age, sex, race, hypertension, hypercholesterolemia, oral glucocorticoid use, and coexisting inflammatory disease did not substantially modify the odds ratio.
a single agent, or group of agents, could be involved in the pathogenesis of both. Together with the observation that patients with CAD do not often develop pulmonary fibrosis, such differences in immunologic response also argue against an inherent predisposition to fibrosis as the principal mechanism.

We favor the third explanation instead, that of a causal relationship wherein pulmonary fibrosis promotes atherosclerosis. Several lines of evidence suggest that the fibroproliferative lung process can exert systemic effects. Levels of cytokines and growth factors, as well as biologically active eicosanoids, have been found to be elevated in the sera or urine of patients with fibrosing lung diseases. The former have been implicated in the hepatic production of acute phase reactants in these disorders. Circulating immune complexes also can be detected in the plasma of patients with IPF. Furthermore, pulmonary fibrosis is associated with the development of vascular proliferation in the digits and mediastinum. Hence, the fibroproliferative process seems to affect cells beyond the pulmonary compartment, and the many mediator molecules produced in these disorders provide multiple potential mechanisms through which they might promote atherogenesis.

**CANDIDATE MOLECULAR PATHWAYS**

Present understanding of immune mediators allows us to speculate on several of the possible candidates. Among them, the cytokines interleukin (IL) 4, tumor necrosis factor α, and IL-13, all of which show elevated levels in pulmonary fibrosis, could lead to atherogenesis in a variety of ways. Interleukin 4 and tumor necrosis factor α can up-regulate cell adhesion molecules that are central to the recruitment of leukocytes to the vascular intima. Also, IL-4 and IL-13 can stimulate cellular lipoxigenases that generate proatherogenic oxidized low-density lipoprotein. Moreover, IL-4 and IL-13 can reduce hyaluronectin secretion, leading to lower levels of this angiogenesis-inhibiting molecule, which could potentially have a proatherogenic effect.

Another prospect is IL-8, a chemokine found in the serum of patients with IPF and sarcoidosis that has proved to be important in the angiogenesis underlying atherosclerotic plaque growth. The notion of a circulating angiogenic factor in pulmonary fibrosis is appealing in light of the common finding of clubbing in IPF, sarcoid-associated fibrosis, and hypersensitivity pneumonitis. Like pulmonary fibrosis and atherosclerosis, clubbing involves neovascularization and fibroplasia. Although impact of circulating megakaryocytes in digital capillaries can explain clubbing in many instances, it is probable that additional factors play a role, and circulating cytokines, including IL-8, remain attractive candidates.

**LIMITATIONS**

A spurious association could have resulted in our population if the referral-for-transplantation threshold for patients with chronic obstructive pulmonary disease and CAD was higher than that for patients with fibrotic lung disorders. There are no clinical grounds to suspect that this would be the case. Alternatively, if patients with smok-
Fifty-seven patients did not undergo coronary angiography. For most patients, this decision was based on age and risk factor prevalence, placing this group at lower likelihood of CAD than the study cohort. The excluded group, however, had a higher proportion of nonfibrinous lung diseases than the cohort that did undergo angiography. Thus, any bias resulting from exclusion of these patients would tend to underestimate the true difference in CAD prevalence between fibrinous and nonfibrinous disorders.

Last, the proposition that fibrictic lung disorders can promote atherosclerosis cannot be confirmed or refuted by a cross-sectional study design. Such a hypothesis can only be tested definitively through longitudinal follow-up, whether in experimental animal models or in human populations, with a clear assessment of incident atherosclerotic disease. Given that pulmonary fibrosis occurs at a relatively advanced stage in humans, pursuit of an epidemiologic study of this kind may be currently infeasible. The association reported herein is an important initial step toward investigating such potential relationships. This investigation should provide impetus for further studies of fibrosing disorders of the lungs and other organ systems in an effort to better understand the inflammatory determinants of the atherosclerotic process and ways in which fibroproliferative disorders throughout the body might be related.

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REFERENCES


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